REMARKS

Claims 1-13 were pending in this case. The Examiner has maintained the rejection of claims 1-13 from the previous Office Action. Applicants amend claim 1 to present the claimed subject matter in clearer terms by introducing the language "a bilayer tablet or a bilayer caplet" and "by separating the ibuprofen and the diphenhydramine." Applicants cancel claims 3, 4, and 5 without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in this or a continuation application. Applicants amend claim 6 to rewrite it in independent form and also to present the claimed subject matter in clearer terms by clarifying that the PEG prevents negative interactions between the ibuprofen and the diphenhydramine. Lastly, Applicants amend claims 7, 8, and 9 to depend from claim 6 instead of claim 1. Support for the claim amendments can be found in the specification as filed, for example, at least at page 13, line 21 to page 14, line 10. No new matter is added.

Applicants also submit a declaration under 37 C.F.R. § 1.132 executed by Dr. James Fort, an inventor in this patent application, to further describe the insufficiencies of the cited art. Applicants respectfully request consideration and examination of this application and the timely allowance of the pending claims 1-2 and 6-13 in view of the arguments below.

Anticipation Rejection Under 35 USC § 102

The Examiner maintains the rejection of claims 1-3 and 7-9 under 35 USC §102(b) as allegedly being anticipated by U.S. Patent No. 4,522,826 to Sunshine *et al.* (hereafter "*Sunshine*"). In particular, the Examiner appears to contend that any prevention of

negative interactions between ibuprofen and diphenhydramine would be inherent in the cited reference. Office Action at page 2.

Applicants respectfully traverse this rejection. A proper anticipation rejection requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. Further, to serve as an anticipation reference in an inherency rejection, the reference must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1376 (Fed. Cir. 2003).

The instant invention is based, at least in part, on the realization that there are negative interactions between ibuprofen and diphenhydramine. As discussed in the specification as-filed, the potential exists for negative interactions between ibuprofen and diphenhydramine. For example, standard tablets or caplets may exhibit dissolution failures, eutectic formation and liquefaction, appearance problems (mottling and peeling), accelerated degradation and potential low potency (active ingredients being lost in the formulation process). These negative interactions may be especially pronounced when the hydrochloride form of diphenhydramine is used. *See,* page 12, lines 8-18, of the specification as filed. For example, a 50:50 composition of diphenhydramine hydrochloride and ibuprofen when taken from a dry to a wet state results in a transformation from a white powder to a translucent gray sticky mass even after it was dried again, with the change in opacity and color indicating that a chemical interaction had occurred. *See*, page 12, line 19 to page 13, line 6 of the specification as filed. One way by which the present invention solves the problem associated with

negative interactions between diphenhydramine and ibuprofen, is by using a bilayer tablet or a bilayer caplet to separate the two compounds. *See* Fort Declaration, ¶ 8.

Claim 1 is directed to a composition comprising ibuprofen and diphenhydramine in amounts effective to treat a pain-associated sleep disturbance, where the composition *is formulated to prevent negative interactions between diphenhydramine and ibuprofen*. It appears that the Office has not taken this limitation of the claimed invention into account, i.e., that the composition is formulated to prevent negative interactions between the ibuprofen and the diphenhydramine. *See* Fort Declaration, ¶ 8.

The Examiner appears to contend that the composition disclosed in *Sunshine* may be formulated as a two-layered tablet. *See* Office Action at page 4. Applicants submit that contrary to the Examiner's allegation, the layered tablets of *Sunshine* are very different from the bilayer tablets of the instant claims, both in structure and in function. First, *Sunshine* discusses layered tablets for a different goal—to achieve active sustained release, not to separate the ibuprofen from the diphenhydramine. For example, according to *Sunshine* at col. 7, line 69 to col. 8, line 6:

> "Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices."

Second, the layered tablets of *Sunshine* do not separate the ibuprofen and the diphenhydramine, but include both ibuprofen and diphenhydramine in each layer. For example, *Sunshine* discusses at col. 8, lines 6-13:

> "[W]ith respect to such layered tablets, one layer may contain an initial dosing amount of, for example, ibuprofen,

> of 400 milligrams and 25 milligrams of diphenhydramine, whereas two or more further layers may contain, for instance, 100 milligrams of ibuprofen and 15 to 25 milligrams of diphenhydramine to be released serially every 4 to 6 hours consistent with the normal dosage schedule."

Accordingly, not only does *Sunshine* fail to recognize that there are potential negative interactions between ibuprofen and diphenhydramine, *Sunshine* in fact includes both ingredients in the same layer of a tablet, allowing the negative interactions to occur. Also, see Fort Declaration, ¶ 9, which discusses that the layered tablets of *Sunshine* contain both active ingredients in each layer and do not physically separate them from each other.

Applicants have amended claim 1 to more clearly define the claimed subject matter by introducing the language "a bilayer table or a bilayer caplet" and "by separating the ibuprofen and the diphenhydramine" into claim 1. Accordingly, this amendment now makes it clear that the negative interactions between the ibuprofen and the diphenhydramine can be prevented by using a bilayer tablet or a bilayer caplet which separates the ibuprofen from the diphenhydramine.

Accordingly, Applicants submit that *Sunshine* does not anticipate the claimed invention, either expressly or inherently, and request that this rejection be withdrawn.

Obviousness Rejection Under 35 USC § 103(a)

Claims 4-6 and 10-13 are rejected under 35 USC § 103(a) as allegedly being obvious over *Sunshine*. The Examiner has maintained this rejection from the previous Office Action, in which the Examiner contended that it would be obvious to one of ordinary skill in the art to modify the composition of *Sunshine* to employ specific salts of

diphenhydramine recited in the claimed invention or use polyethylene glycol in the compositions of the invention.

Applicants have canceled claims 4 and 5, thereby rendering this rejection moot with respect to those claims. Claim 6, which now is rewritten in independent form recites a soft gelatin capsule containing polyethylene glycol. Claims 10-13 depend directly or indirectly from claim 1 and are directed to compositions including ibuprofen and specific salts of diphenhydramine, such as, for example, diphenhydramine hydrochloride (claims 10 and 11) and diphenhydramine citrate (claims 12 and 13). Applicants traverse this rejection and provide the following arguments in view of the claims as amended.

As discussed above, the potential for negative interactions exists between ibuprofen and diphenhydramine when they are contained in a standard tablet or capsule. Another way to solve the potential problem is by formulating the ingredients as a soft gelatin capsule in combination with polyethylene glycol, which is believed to protect against this interaction. *See* Fort Declaration, ¶ 8.

Applicants submit that contrary to the Examiner's contention, *Sunshine* fails to provide any motivation to use polyethylene glycol in the compositions of the invention to prevent negative interactions between ibuprofen and diphenhydramine. *See* Fort Declaration, ¶ 10.

First, as discussed above, *Sunshine* fails to even recognize that there are negative interactions between ibuprofen and diphenhydramine, let alone suggest ways by which these interactions can be prevented. Thus, *Sunshine* provides no motivation

to specifically include polyethylene glycol to prevent negative interactions between the ingredients.

Second, *Sunshine* mentions polyethylene glycol only as a suitable binder among a laundry list of binders. For example, *Sunshine* discusses at col. 7, lines 30-33:

> "Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes."

Applicants note that the laundry list of binders in *Sunshine* includes several genuses of binders (e.g., waxes, natural sugars, natural and synthetic gums) and specific species (e.g., sodium alginate, polyethylene glycol), thereby providing a plethora of choices for selection. *Sunshine* fails to provide any motivation to pick a particular binder from the list. Courts have generally held that a prior art reference containing a "needle-in-the-haystack" type disclosure does not render a patent obvious. *See*, for example, *In re Luvisi*, 342 F.2d 102, 105; 144 U.S.P.Q. 646, 649 (C.C.P.A. 1965).

In *Luvisi*, the claimed invention related to a process for killing undesired vegetation and compositions for accomplishing the same, which had some synergistic properties. The claimed composition in *Luvisi* included two essential ingredients. The Patent Office Board of Appeals rejected the claimed composition as being obvious in view of a primary reference which disclosed a list of compounds, about fifty in number, including one of the compounds that could be used in the claimed composition, in combination with a secondary reference, which disclosed a second compound of the claimed composition. The Court in *Luvisi* reversed the obviousness finding of the Board and reasoned that the primary reference contained a "needle-in-the-haystack"

disclosure. There was nothing in the primary reference that would suggest combining a particular compound from the list of fifty compounds with a compound disclosed in the secondary reference, nor any disclosure teaching that the resulting composition had synergistic properties. The Court further discussed that while it was possible to piece together isolated features of patentee's invention taken from the cited references with the aid of patentee's disclosure, that the invention would not have been obvious in the absence of such disclosure. Specifically, the Court stated "[W]hereas a brief and selective presentation of the teachings of the art of record, such as that outlined . . . may cause such a conclusion to appear reasonable, we believe it becomes so only through hindsight reasoning." *Luvisi* at 1067.

Applying this precedent to the instant case, Applicants note that there is nothing in *Sunshine* that would suggest specifically using polyethylene glycol, listed among five genuses and six species of binders, in compositions of the claimed invention for preventing negative interactions between ibuprofen and diphenhydramine. Further, as in case of *Luvisi*, even though *Sunshine* lists isolated pieces of the claimed invention (i.e., ibuprofen, diphenhydramine and PEG), it would be possible to combine them only in hindsight, based on the instant specification.

Applicants submit that polyethylene glycol has special properties not recognized by *Sunshine* and divergent from the remaining binders and classes of binders in the laundry list. *Sunshine* fails to direct one of ordinary skill in the art to polyethylene glycol. Accordingly, Applicants submit that it is improper for the Examiner to pick and choose polyethylene glycol from the list of binders in hindsight, as a mere list of compounds in *Sunshine* does not direct one of ordinary skill in the art to polyethylene glycol.

Additionally, *Sunshine* also fails to provide an expectation of success. Not only does *Sunshine* fail to provide any motivation to pick polyethylene glycol from the list of binders, but based on *Sunshine*, one of ordinary skill in the art would not expect polyethylene glycol to prevent negative interactions between ibuprofen and diphenhydramine, as *Sunshine* does not even recognize the potential for such negative interactions.

For example, in *In re Kratz*, 592 F.2d. 1169, 1174; 201 U.S.P.Q. 71, 76 (C.C.P.A. 1979), the Court reversed an obviousness rejection and reasoned that there was nothing in the prior art that taught or gave a reasonable expectation that using a specific chemical would yield a certain result. The facts of the instant case are similar to those in *Kratz*. In *Kratz,* the invention related to a process for imparting a strawberry flavor to foodstuff by adding a certain compound derived from strawberries. Although, the prior art disclosed the same ingredient in nature, the Court noted that there was no basis in the prior art for selecting the specific compound from a list of compounds in strawberries and using it in the claimed composition. The Court concluded that even if the list of such compounds was in the prior art, those lists are mute in directing one of ordinary skill in the art to a particular compound, i.e., which compound in strawberries provided the flavor. *Kratz* at 76. Furthermore, the Court indicated that "[w]hile recognizing that obviousness does not require complete predictability . . . , that the prior art itself provide some foreseeability or predictability that a compound is a significant strawberry flavor ingredient." *Id.*

As in the case of the prior art in *Kratz*, Applicants note that *Sunshine* also fails to direct one of ordinary skill in the art to a particular binder, i.e., polyethylene glycol.

Accordingly, just because *Sunshine* lists polyethylene glycol as a binder that can be used for binding purposes, it does not provide any expectation that polyethylene glycol can be used to prevent negative interactions between ibuprofen and diphenhydramine.

In view of the foregoing, Applicants submit that based on the disclosure of *Sunshine*, one of ordinary skill in the art would have no motivation to specifically use polyethylene glycol to prevent negative interactions between ibuprofen and diphenhydramine. Further, there is also no expectation of success as even if polyethylene was included, based on *Sunshine*, there would be no expectation that negative interactions will be prevented, as *Sunshine* does not even recognize the potential for negative interactions between ibuprofen and diphenhydramine.

In view of the foregoing, Applicants submit that claimed invention is not obvious in view of the cited art and that the pending claims are in condition for allowance.

CONCLUSION

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing all the pending claims in condition for allowance. Applicants submit that the proposed amendments to the claims do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimer or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner. Additionally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is not rendered obvious in view of the references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims. Should the Examiner feel that this application is not in condition for allowance, Applicants request that the Examiner contact the undersigned representative at 202-408-4086.

If there is any fee due in connection with the filing of this Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 23, 2004

By: Rebecca M. McNeill
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PATENT
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Attorney Docket No. 01142.0125-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

COOK et al.

Application No.: 10/046,727

Filed: January 17, 2002

For: TREATMENT OF SLEEP DISTURBANCES

Group Art Unit: 1617

Examiner: Jennifer M. Kim

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, James J. Fort, do hereby make the following declaration:

1. I am an inventor of the above-captioned application. My curriculum vitae is attached to this declaration as Exhibit 1. My field of expertise is the formulation and development of novel drug compositions. I have specific expertise in the formulation of drug compositions and analysis of drug interactions, based on my education and fifteen years of experience at two pharmaceutical companies.

2. I have read the Office Action dated March 23, 2004, and I understand that Examiner concludes that the disclosure of the U.S. Patent No. 4,552,826 to Sunshine (hereafter "*Sunshine*") anticipates claims 1-3 and 7-9 and renders claims 4-6 and 10-13 obvious to those skilled in the art as of the filing date of the instant application.

3. I believe that the compositions of the instant application are not disclosed, expressly or inherently, in *Sunshine*. Further, I believe that one of ordinary skill in the

art will not be motivated to modify or combine the compositions disclosed in *Sunshine* to arrive at the claimed invention.

4. *Sunshine* describes a prophetic composition comprising an analgesic/anti-inflammatory agent, such as ibuprofen (*see*, column 6, lines 39-50), and a sleep-inducing agent, such as diphenhydramine (*see*, column 7, lines 46-60). *Sunshine* also discusses concomitant administration orally of ibuprofen and diphenhydramine solutions or suspensions to mice by gavage, and an enhanced analgesic effect in mice upon this administration. (*See*, Example 1). *Sunshine* only discusses administration of combinations of separate doses of ibuprofen and diphenhydramine to mice. *See*, column 10, Table 2.

5. *Sunshine* fails to provide any working examples of tablets or capsules that include ibuprofen and diphenhydramine.

6. It has been shown that there are negative interactions between ibuprofen and diphenhydramine when they are contained in a standard tablet or caplet, including dissolution failures, eutectic formation and liquefaction, appearance problems (mottling and peeling), accelerated degradation and potential low potency (active ingredients being lost in the formulation process). For example, a 50:50 composition of diphenhydramine hydrochloride and ibuprofen when taken from a dry to a wet state results in a transformation from a white powder to a translucent gray sticky mass even after it was dried again, with the change in opacity and color indicating that a chemical interaction had occurred. *See*, page 12, line 19 to page 13, line 6 of the specification as filed.

7. The instant invention is directed to formulations that are created to prevent undesirable negative interactions between ibuprofen and diphenhydramine and include, for example, pharmaceutical formulations, such as, bilayer tablets and soft gelatin capsule containing polyethylene glycol. (*See*, for example, pages 12-14 of the specification as filed). The bilayer tablets or caplets of the instant invention physically separate ibuprofen and diphenhydramine, thereby preventing any negative interactions between the two compounds. The present invention also solves the problem associated with negative interactions between diphenhydramine hydrochloride and ibuprofen by using soft gelatin capsules containing these compounds in combination with polyethylene glycol, which is believed to protect against this interaction. *Sunshine* does not specifically disclose any compositions of ibuprofen and diphenhydramine that are formulated to prevent negative interactions between the two compounds.

8. *Sunshine* does not even contemplate the problem associated with the negative interactions between ibuprofen and diphenhydramine and suggests ordinary tablets. I believe that the layered tablets described in *Sunshine* (*see* column 8, lines 6-13), which contain ibuprofen and diphenhydramine in the same layer, will not prevent negative interactions between ibuprofen and diphenhydramine. Specifically, column 8, line 4 of *Sunshine* states that "one layer may contain an initial dosing amount of, for example, ibuprofen, of 400 milligrams and 25 milligrams of diphenhydramine, whereas two or more further layers may contain, for instance, 100 milligrams of ibuprofen and 15 to 25 milligrams of diphenhydramine." These bilayered tablets contain ibuprophen and diphenhydramine in **both** layers. Accordingly, Applicants submit that the layered tablets described in *Sunshine* are different from the bilayer tablet or bilayer caplet of claim 1,

which separates the ibuprofen from the diphenhydramine, thereby preventing negative interactions between the two. The layered tablets of *Sunshine* contain both active ingredients in each layer and do not physically separate them from each other.

9. Additionally, *Sunshine* does not recognize the potential advantages of formulating a capsule using PEG to prevent negative interactions between ibuprofen and diphenhydramine. *Sunshine* includes PEG in a laundry list of possible binders including:

> starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes

(col. 7, lines 30-33), the remainder of which would not prevent negative interactions between ibuprofen and diphenhydramine. Considering the teachings of *Sunshine*, there would have been no reason for the person of ordinary skill in the art to select PEG from amongst the other binders taught. *Sunshine* did not teach this particular combination, nor did it point out any advantages to using PEG from amongst the laundry list of binders.

10. Finally, I believe that the instant invention solves problems associated with tablet formulations by preventing negative interaction between compounds in a tablet or caplet, thereby extending the shelf-life of the tablet.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under

Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: August 23, 2004

By: _____
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EDUCATION

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PUBLICATIONS/PRESENTATIONS/PATENTS

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